

## Invited Editorial

### In Defense of Science

This essay was to accompany the Professor Merry Lecture at the Perfusion Downunder Winter meeting, Queenstown, New Zealand, August 2021. Due to the COVID-19 pandemic, the meeting has been postponed to August 2022.

#### TRIUMPH

For much of human history, life expectancy was about 30 years. Even as late as 1800, in no country did life expectancy exceed 40 years (1). Half of all children died before reaching adulthood and the great majority of the world's population lived in poverty. Life, in the words of English clergyman Thomas Hobbes, was “nasty, brutish, and short.” Then, over the last 150 years, something remarkable happened. Across the globe, people started living longer, healthier lives. In the years from 1870 to 2019, life expectancy in England and Wales more than doubled from 40 years to over 80 years. Similar increases were observed in Europe, Japan, North America, and Oceania. In the developing world, change came later but has been no less impressive. In 1925, life expectancy in Africa was a mere 26 years but by 2019 had increased to over 63 years (1). Without doubt, we are living in the best of times.

Many factors contributed to this transformation: improved living standards, food security, access to clean drinking water and to sanitation, advances in healthcare, and the establishment of public health practices and institutions. But underpinning all of these developments are three simple principles: knowledge, science, and technology (2). Nowhere is this winning combination more evident than with vaccines.

On the 14th of May 1796, Edward Jenner inoculated an 8-year-old boy, James Phipps, with cowpox using scrapings from blisters on the hands of milkmaid Sarah Nelmes. In doing so, Jenner not only protected the lad against smallpox but ushered in the age of vaccination. By 1900, just 23 years after Louis Pasteur proposed his germ theory of disease, vaccines were available against smallpox, cholera, typhoid, rabies, and plague. Diphtheria antitoxin, first discovered by Emile Roux in 1888, went into mass production in 1893.



David Sidebotham, MB, ChB, FANZCA

It is hard to overstate the impact of vaccines. In the United States, vaccines have led to a 98% reduction in nine transmissible diseases (3). In 2019, 86% of infants worldwide received three doses of the DTP 3 (diphtheria, tetanus, pertussis) vaccine, a staggering achievement, saving some four million lives annually. In the words of Dr. Tedros Adhanom Ghebreyesus, Director General of the World Health Organization, “Vaccines are one of the most powerful tools in the history of public health, and more children are now being immunized than ever before” (4).

And now we are witness to one of the greatest achievements in all of medical science: the development of safe and effective vaccines against SARS-CoV-2, the coronavirus that causes COVID-19. The timeline is astonishing. On January 10, 2020—the same day that

Chinese authorities released the genetic sequence—German company BioNTech began work on a novel RNA vaccine against SARS-CoV-2. Partnering with U.S. pharmaceutical giant Pfizer, clinical trials began in April. Then, on December 2, some 11 months after work first started, the UK authorized emergency use of tozinameran, the Pfizer-BioNTech vaccine. A few months later, vaccines from Moderna, Oxford-AstraZeneca, and others completed clinical trials and were approved for use. At the time of writing, there are eight vaccines in clinical use against SARS-CoV-2, with 32 undergoing phase III trials, and a further 53 in development (5). By contrast, the first experimental polio vaccine was produced in 1935 but it was two decades later that the Salk and Sabin vaccines, in 1953 and 1956, respectively, were introduced into widespread use.

## TRAGEDY

However, all is not well. Currently, there have been more than 200 million confirmed cases of COVID-19 and over four million deaths (6). The true numbers are certainly much higher. Less than a third of the world's population is fully vaccinated. There are huge disparities in vaccine availability between wealthy and poor countries. The United Nations estimates that the COVID-19 pandemic could displace more than 150 million people into extreme poverty (7). Around the world, childhood vaccination programs have been severely disrupted. In the United States, life expectancy fell by 18-months in the first year of the pandemic.

And worryingly, in a time when knowledge, science, and technology are most relevant they are under unprecedented attack. Self-serving leaders distort, obfuscate, and undermine science. Anti-science conspiracy theories abound, amplified by social media companies whose algorithms channel millions of people into toxic echo chambers of disinformation. Television personalities undermine vaccine safety while the unvaccinated get sick and die. Lifesaving public health measures have become a proxy battle of the culture wars. Scientific leaders are targets of hate. The Age of Reason seems diminished.

## THE CHALLENGE

What can we, as clinicians and scientists, do? First, we should acknowledge our good fortune. We have all benefited greatly from scientific progress and technological development. I am 55 years old. It is a miracle I am even alive. At every opportunity and using every available platform, we should champion scientific

achievement. However, to better defend science, we should know what drives science denial and we should understand why sometimes things go wrong. And, occasionally, things do go terribly wrong. In 1955, in what is now known as the Cutter Incident, polio vaccine was contaminated with live virus leaving 51 children paralyzed and killing five (8). We must learn from our failures and we must strive not to repeat them. Finally, since it is impossible to know anything with absolute certainty—except perhaps in pure mathematics—we should understand and embrace uncertainty.

## DENIAL

In 2019, a friend of mine, Alan McClintic—who, sadly, has since died—wrote a powerful editorial exploring the origins and motivations of science denial (9). The article preceded the COVID-19 pandemic and was written in response to a measles outbreak in New Zealand and the Pacific Islands that claimed more than 80 lives, mostly in Samoa. McClintic identified several factors driving mistrust and skepticism of science, including a lack of knowledge, conspiracy thinking, politicization, and profit. However, for me, one cause stands out: cultural cognition. Cultural cognition refers to the “deeply ingrained values and beliefs that give us our sense of self, group identity, and how we want society to be.” As McClintic makes clear, “if science threatens that worldview it will tend to be the science that is dismissed rather than the worldview.” In this context, “the greater a person's knowledge of science the greater their resistance to that science.” In one illustrative example, when vaccine-hesitant parents were provided with information on the safety and effectiveness of vaccines they became even more convinced not to vaccinate their children (10).

Cultural cognition is difficult—frequently impossible—to overcome, but three things may help. First, providing information in a narrative form rather than as a series of facts—telling stories that people can relate to. Second, views from within a cultural group may be more readily accepted by members of that group than views expressed by outsiders. Recently, prominent conservative radio host Phil Valentine died of complications related to COVID-19. Prior to contracting the disease, Valentine had been an outspoken critic of vaccination and mask wearing. However, once diagnosed he reversed his position and pledged to be vigorously pro-vaccination. Had he survived, Valentine would likely have been more effective in preventing COVID-19 amongst his listeners than either Anthony Fauci or Tedros Adhanom Ghebreyesus. Finally, the acceptance of science is undermined when the scientific community

itself appears divided. Scientists and public figures must provide consistent messaging, focusing on the existential threat and ignoring the petty squabbles that drive the 24-hour news cycle.

## THE METHOD

Based on the concept of empiricism—that knowledge comes from experience rather than reasoning—the scientific method is the cornerstone of knowledge acquisition in science. It works like this. We formulate a hypothesis from which a logical, testable prediction arises. Here we can equate “testable” with “falsifiable,” the capacity to prove the prediction wrong. We perform an experiment to test the prediction. We analyze the data. If the data refutes the prediction, we revise the hypothesis. If the data support the prediction, we have evidence in favor of the hypothesis. If sufficient data accrue, we accept the hypothesis as true.

Causality is hard to prove. A lot of data from many experiments are required to convert a question (Does smoking cause lung cancer?) into a statement (Smoking causes lung cancer). Not every question of interest can be answered. It is impossible to design experiments for hypotheses that do not yield testable predictions. Such is the situation in much of modern theoretical physics. In the words of Wolfgang Pauli, such theories are “not even wrong” (11).

## SABOTAGE

The scientific method can be subverted, and it can fail. Experiments may be badly designed. Treatments may be given in the wrong dose at the wrong time to the wrong people. Bias can occur at any stage—in the conduct of the trial, in the analysis of the data, and in the way the results are reported, interpreted, disseminated, and acted upon.

Randomized trials rightly sit at the top of the evidence hierarchy. Random treatment allocation avoids selection bias, which bedevils other study designs. While a clear association between blood transfusion and adverse outcome has been observed in multiple non-randomized series, it is difficult to know whether transfusion *causes* adverse outcome or whether transfusion and adverse outcome are linked by a “third man.”\* Perhaps, the new science of causal inference will help us better tease out causal relationships from large datasets (12). Meantime, we continue to rely on randomized

trials as the foundation of evidence-based medicine. Unfortunately, randomized trials are not immune from bias. In a recent review of cancer trials, almost half were found to be at high risk of bias (13). In a review of trials in perioperative medicine, more than half were unblinded (14).

P-hacking is the process of trawling through datasets looking for statistically significant differences (15). As the economist Ronald Coase once observed, “If you torture the data for long enough, it will confess to anything.” Trial registration, in which outcomes are prespecified, is meant to prevent P-hacking. However, only about half of randomized trials are registered (16), and even when trials are registered, reported outcomes frequently differ from planned outcomes (17,18). Publication bias, whereby trials reporting significant results are more likely to be published than trials reporting non-significant results, distorts the literature, favoring positive results over the truth. Publication bias exists across all areas of science, including in my own specialty (19).

Rarely, researchers falsify or concoct data. Two recent high-profile retractions, one in the *Lancet* and the other *New England Journal of Medicine*, received widespread publicity (20). Such events undermine public confidence in science, but how common are they? John Carlisle, a UK anesthesiologist, used anomalies in the distributions of baseline characteristics (e.g., age, height, weight) reported in over 5,000 randomized trials in six anesthesia journals and two high-impact general medical journals to identify potentially fabricated data (21). He identified potential fraud in 1.6% of unretracted trials. So, not common but not uncommon enough.

The term “paper mill” describe a process whereby fraudulent manuscripts are submitted for publication on behalf of clinicians and scientists. In some cases, data are plagiarized from legitimate publications, in other cases data are entirely fabricated (22). The scammers also subvert the peer review process by offering “expert” reviewers. In but one example, in 2017, 107 potentially fraudulent studies were retracted by a single journal, *Tumor Biology* (23).

None of this is helped by an explosion of predatory journals—journals that exist solely to make money through processing fees (24). Every day, my inbox is filled with messages that read, “Dear esteemed colleague, greetings of the day...,” followed by an invitation to submit an article—on any topic—to the *Journal of Scientific Advancement and Case Reports* or some such, which guarantees seamless 24-hour peer review and unprecedented exposure for my valued contributions. But even in the top journals, the peer review process is not fit for purpose. In one study, involving reviewers for the *British Medical Journal*, fewer than a

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\*The third man is a term coined by Professor Paul Myles for unmeasured confounding variables.

third of deliberately placed errors were identified in manuscripts sent for review (25).

## POWER

When we do experiments, we analyze data from samples and attempt to draw inferences about the population from which the samples are drawn. Null hypothesis significance testing is the dominant framework for statistical inference that is used in medical research (26). We calculate  $p$ -values and confidence intervals (CIs) to quantify the extent to which the data provide evidence against the null hypothesis (the falsification principle mentioned earlier). When  $p$  is less than or equal to some predefined value ( $\alpha$ ) or the CI excludes the null value, we reject the null hypothesis and rightfully claim the result to be statistically significant. Because statistics is based on the rules of chance, even when things work perfectly, we *expect* the test to be wrong some of the time. However, things do not work perfectly. While bias and fraud can influence the outcome from statistical testing, there is a bigger problem: low power.

Statistical power is the chance the test will be significant when a real effect exists. When designing a trial, researchers calculate the sample size that is required to achieve adequate power. Adequate power is generally taken to mean at least 80%. Calculating the sample size also involves choosing a value for the effect size that might exist in the population. The larger the effect size, the smaller the sample size that is required to achieve the same power. Recruiting large sample sizes is expensive and logistically challenging. It is tempting, therefore, to overestimate the effect size. In medical research, overestimating the effect size is so common as to be routine (27–30). Consequently, the actual power of many studies is far lower than the power reported in the published report.

When power is low things get very sketchy. First, an alarming proportion of results are false. That is to say, the chance a real effect exists when the test is significant is low and the chance a real effect exists when the test is non-significant is high (26,30,31). The contrarian epidemiologist John Ioannidis estimates that more than half of all published research findings are false (31). Second, the  $p$ -values from repeated sampling vary widely, meaning there is poor concordance between studies investigating similar interventions (32). It is unsurprising then that science has something of a reproducibility crisis (33,34).

## FRAILITY

As clinician scientists, we are both noisy and biased. Noise is the scatter opinions or beliefs that arise when the truth is subjective, unknown, or unknowable. I recently

asked my colleagues a question: “If you knew for certain how effective extracorporeal membrane oxygenation was for treating severe pneumonia, what is the smallest reduction in absolute mortality that would make you recommend the treatment?” The answers ranged from 2% to 20%, a 10-fold difference. Pretty noisy.

This example also illustrates another important point: we humans are terrible natural statisticians. Our brains do not intuitively grasp probabilities. For instance, the risk of developing cerebral venous thrombosis—a potentially fatal complication—from the AstraZeneca COVID-19 vaccine is around 5 per million people (35). Expressed as a probability, 5 per million is .000005. By contrast, the risk of developing cerebral venous thrombosis from COVID-19 *infection* is around 39 per million people (.000039) (35). Our brains cannot readily distinguish between a probability of .000005 and .000039 but we have no difficulty understanding that it possible to develop potentially fatal blood clots from a vaccine. In reality, the risk of dying from COVID-19 is several thousand times higher than the risk of dying from a COVID-19 vaccine.

Cognitive biases are systematic errors in the way we process information. Confirmation bias is the tendency to interpret information in a way that conforms to our prior beliefs. Take the ADRENAL study, a large multicentre trial comparing hydrocortisone with placebo in patients mechanically ventilated for septic shock (36). ADRENAL is one of several studies over the last 20 years investigating whether corticosteroids benefit critically ill patients. Most intensivists have an opinion but there is no consensus. There is a lot of noise. The main finding from ADRENAL was that mortality was almost identical in the hydrocortisone and placebo groups. However, statistically significant differences were apparent amongst secondary outcomes. Patients assigned to hydrocortisone had faster resolution of shock and a shorter duration of mechanical ventilation than those assigned to placebo. Like the Fatman in Samuel Shem’s *The House of God* (“If I was you Potts, I’d give him some ‘roids’”), I think corticosteroids are useful in septic patients. I also know that hardly any trial in critical care has shown a mortality benefit (30). As such, ADRENAL confirmed my preconceived notions: those secondary outcomes are worth a second look. Yet, for my steroid-skeptical colleagues, ADRENAL confirmed what they always knew: steroids don’t save lives.

Before moving on, two other cognitive biases are worth mentioning: apophenia bias and self-serving bias. Apophenia is the tendency to perceive meaning in random noise (37). A consequence of apophenia bias is that we are naturally inclined to believe statistically significant results. Self-serving bias is the tendency to take credit for positive outcomes and blame others for

negative outcomes. In 2015, a study was published in *Anesthesia and Analgesia* showing that the anesthesiologist was an independent predictor of outcome from cardiac surgery (38). I found the result deeply appealing. First, the result was highly significant (apophenia bias). Second, as a cardiac anesthesiologist, I felt validated (self-serving bias). Researchers had finally confirmed what I knew all along: I matter. Unfortunately, my exuberance was misplaced. In error, the authors used the wrong statistical model. The effect disappeared when the correct model was applied. When the paper was retracted, I felt deflated. Although, perhaps, not as deflated as the authors, who made an honest mistake.

## HOPE

It may seem self-defeating to spend most of an article entitled *In Defense of Science* pointing out its weaknesses. That is not my view. We must be honest about our failings. We must put our house in order and do the best science that we can. Eliminating fraud, bias, and underpowered studies will increase the efficiency with which we acquire knowledge and reduce the chance of causing harm, but it will not stop us from being wrong. For being wrong is part of how science works. The beauty of the scientific method is that it is self-correcting. False hypotheses are discovered to be false, and new hypotheses are formulated and tested. Slowly, we stumble towards the truth.

The first clinical use of cardiopulmonary bypass was by John Gibbon in 1955. Now, some 65 years later, more than a million cardiac surgical procedures are performed each year. It seems natural that a child born with a ventricular septal defect (VSD) would undergo surgical repair. But it is anything but natural. Consider the cumulative knowledge of each craft group involved—surgeon, perfusionist, anesthesiologist, cardiologist, echocardiographer, theater nurse, intensive care unit (ICU) nurse, intensivist, etc. Consider the precision engineering and electronic circuitry of modern machines used for anesthesia, cardiopulmonary bypass, echocardiography, postoperative ventilation, blood gas analysis, etc. Each one working flawlessly, time after time after time. Consider the scientific discoveries. The piezoelectric effect used in ultrasound transducers, first demonstrated by Jacques and Pierre Curie in 1880. The development of gas permeable membranes by Clowes and Neville in 1955 that paved the way for modern oxygenators (39). The cephalosporin producing mold discovered by Giuseppe Brotzu near a sewage outfall in 1945. In fact, consider the many thousands of scientific studies done over the last 65 years, so that a child born with a VSD can expect

to live a full and active life. It is a towering achievement and one I am privileged to be a part of.

This week I have been looking after patients with COVID-19 in the ICU. Compared to the start of the pandemic, less than 2 years ago, we now have evidence-based interventions that improve patient survival. I am fortunate enough to be fully vaccinated and to have ready access to personal protective equipment. Already, the science of preventing and treating COVID-19 has come a long way in a very short time. Through science, we have solved many problems and improved countless lives. I have every reason to think we will continue to do so. We have no alternative—it's the only game in town.

David Sidebotham, MB, ChB, FANZCA  
Anesthesiologist and Intensivist

Department of Anaesthesia and the Cardiothoracic and Vascular Intensive Care Unit

Auckland City Hospital

Auckland, New Zealand

E-mail: dsidebotham@adhb.govt.nz

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